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Uppermost synchronized generators of spike–wave activity are localized in limbic cortical areas in late-onset absence status epilepticus

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ABSTRACT

Purpose: Absence status (AS) epilepticus with generalized spike–wave pattern is frequently found in severely ill patients in whom several disease states co-exist. The cortical generators of the ictal EEG pattern and EEG functional connectivity (EEGfC) of this condition are unknown. The present study investigated the localization of the uppermost synchronized generators of spike–wave activity in AS.
Method: Seven patients with late-onset AS were investigated by EEG spectral analysis, LORETA (Low Resolution Electromagnetic Tomography) source imaging, and LSC (LORETA Source Correlation) analysis, which estimates cortico-cortical EEGfC among 23 ROIs (regions of interest) in each hemisphere.
Results: All the patients showed generalized ictal EEG activity. Maximum *Z*-scored spectral power was found in the 1–6 Hz and 12–14 Hz frequency bands. LORETA showed that the uppermost synchronized generators of 1–6 Hz band activity were localized in frontal and temporal cortical areas that are parts of the limbic system. For the 12–14 Hz band, abnormally synchronized generators were found in the antero-medial frontal cortex. Unlike the rather stereotyped spectral and LORETA findings, the individual EEGfC patterns were very dissimilar.
Conclusion: The findings are discussed in the context of nonconvulsive seizure types and the role of the underlying cortical areas in late-onset AS. The diversity of the EEGfC patterns remains an enigma. Localizing the cortical generators of the EEG patterns contributes to understanding the neurophysiology of the condition.

1. Introduction

Long-lasting ictal epileptic conditions with deranged higher-order cerebral functions but not major convulsions are labeled as nonconvulsive status epilepticus (NCSE). NCSE with generalized spike–wave pattern is usually called absence status (AS). AS may appear as a complication of idiopathic and symptomatic epilepsies[1] and may be precipitated by acute cerebral disorders, metabolic-toxic conditions, neuroactive drugs, a few antibiotics, hormonal changes, fever and sleep deprivation.[2–4] AS may occur in severely ill patients in whom several pathological conditions co-exist.[5,6] The diagnosis of AS may be suspected on clinical grounds but should be confirmed by an ictal EEG record.

NCSE was at first subdivided into generalized (absence status, spike–wave stupor) and focal (psychomotor status, complex partial status epilepticus) groups. This rigid dichotomy has been challenged by a lot of observations. Well-documented reports revealed that ictal EEG activity frequently starts focally and becomes bilateral and synchronous later, in the course of AS.[7,8] Conventional analysis of the EEG potential field only allows raw topographical estimation of the cortical generators when the ictal patterns are bilateral. Furthermore, it is not known what sort of abnormal EEG functional connectivity (EEGfC) of the brain is associated with the derangement of higher cerebral functions in AS. Neurophysiological exploration of the severely ill patients with AS has not been carried out yet. EEG source analysis may be

Abbreviations: AS, absence status; BOLD, blood-oxygen-level-dependent; EEGfC, EEG functional connectivity; LORETA, Low Resolution Electromagnetic Tomography; LSC, LORETA Source Correlation; NCSE, nonconvulsive status epilepticus; ROI, region of interest; VNB, very narrow band.

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Table 1
Main relevant clinical data, laboratory and cranial CT abnormalities of the patients. LH = left hemisphere; RH = right hemisphere.

Pt. no.	Age (sex)	Main clinical data
1	51 (M)	Past history: schizophrenia, moderate mental retardation, rare convulsive seizures. Recent history: upper airway infection with high fever, not specified changes in psychiatric drug treatment, repeated convulsive seizures. Generalized rigidity, somnolence, psychomotor slowing. Findings: CT: mild bilateral temporal-insular atrophy. Mildly elevated blood glucose level. Chronic treatment: carbamazepine but subtherapeutic serum level. Acute drug treatment: no neuroactive drugs before EEG registration.
2	82 (M)	Past history: hypertension, cardiomyopathy, RH ischemic insult, a single acute symptomatic seizure. Recent history: cranial trauma, RH contusion, subdural hematoma. Two days after evacuation of the hematoma disorientation, followed by motionless, areactive state, the lack of any cooperation. Findings: CT: small RH intracerebral hematoma, overall cortical atrophy. No significant laboratory alterations. Chronic treatment: no neuroactive drugs. Acute drug treatment: no neuroactive drugs before EEG registration.
3	69 (F)	Past history: schizophrenia, ischemic lesion in the LH, three convulsive seizures, diabetes (treated). Recent history: headache, disoriented state, a few hours later motionless, areactive state. Findings: CT: moderate cerebral atrophy. Moderately elevated blood glucose. Chronic treatment: no neuroactive drugs. Acute drug treatment: no neuroactive drugs before EEG registration.
4	82 (F)	Past history: hypertension, ischemic cardiomyopathy, diabetes, focal epilepsy with LH focus. Recent history: right facio-brachial motor seizures, 10 mg diazepam intravenously, followed by motionless, unresponsive state. Findings: CT: Diffuse cortical atrophy and multiple small ischemic lesions in both hemispheres. Moderately elevated blood glucose. Urine analysis indicated purulent uroinfection. Chronic drug treatment: gabapentin, daily dose: 1200 mg. Acute drug treatment: no neuroactive drugs before EEG registration.
5	32 (F)	Past history: childhood absence epilepsy, in terminal remission. Later depression, alcohol abuse and suicide attempt. Diabetes with hypoglycemic episodes and situation-related convulsive seizures. Recent history: upper airway infection, a convulsive seizure, thereafter decreased level of vigilance, no spontaneous movements. Findings: normal cranial CT and laboratory findings. Chronic treatment: no neuroactive drugs. Acute drug treatment: no neuroactive drugs before EEG registration.
6	42 (M)	Past history: no significant disease events. Recent history: high fever, non-purulent encephalitis, several convulsive seizures, disoriented in the intervals. Phenytoin given intravenously abolished the motor seizures but the patient remained confused and areactive. Findings: cranial CT was normal, analysis of the cerebrospinal fluid confirmed aseptic meningitis. Chronic treatment: no neuroactive drugs. Acute drug treatment in the 2 days before EEG registration: intravenous phenytoin, therapeutic serum levels.
7	56 (M)	Past history: long-lasting alcohol abuse and dependence, cerebral and cerebellar atrophy, frontal lobe symptoms. Recent history: hypertonic crisis, left faciobrachial convulsion, benzodiazepine and phenytoin treatment followed by decreased ventilation. Moderately elevated temperature. Confused state and fluctuating level of vigilance. Findings: cranial CT: left temporal hypodense abnormality of unknown origin. No significant laboratory findings. Chronic treatment: no neuroactive drugs. Acute drug treatment a few hours before EEG registration: intravenous diazepam and phenytoin.

performed in the time and frequency domains. However, the former approach does not refer to EEG frequencies and frequency bands. Investigating the frequency domain is of interest in all brain states because brain functions are organized by oscillations at specific frequencies that are strongly interrelated. With these facts in mind we performed EEG source analysis in the frequency domain. Functional connectivity analysis is a particularly important approach because it demonstrates normal and abnormal interrelatedness among parts of a neuronal system or network. Network analysis is a promising tool to realize abnormal functions and clinical symptoms in terms of network dynamics.[9] As to address these issues, we analyzed the ictal EEG activity of seven, severely ill patients with AS.

2. Patients and methods

2.1. Patients and EEG recording

Patients with AS were enrolled into this retrospective study. Using the search words "generalized" and "NCSE" we detected 14 patients in the database of our EEG Laboratory in the 2005–2010 time period. Out of them, seven, non-consecutive patients fulfilled the inclusion criteria for this study: a correct patient file; a good quality EEG record that allows quantitative EEG analysis; the reviewed case had to fit the diagnostic criteria of AS.[10] The presence of active, idiopathic generalized epilepsy was an exclusion criterion. Relevant events of the patients' medical history, clinical, laboratory and cranial CT findings, neuroactive medication and a brief description of the patients' behavior during AS are briefly summarized in Table 1. As far as it is known from the patient's records their medications were not change during the last few days prior to the occurrence of AS.

Six patients had at least two neurological disorders in their past history. Five of them had focal epilepsy or acute symptomatic seizures. Their recent history was very diverse, including some of the following items: recently acquired cerebral lesion, upper airway infection, primary cerebral infection, elevated blood glucose, changes in neuroactive drug regimen, convulsive epileptic seizures. The core symptoms of the AS were very similar in five patients: motionless, unresponsive state, the lack of verbal and nonverbal communication. However, some degree of arousability was preserved. One of the remaining patients had psychomotor slowing and decreased responsiveness (Patient 1), while the other showed fluctuating somnolence and confusion (Patient 7).

All the EEG records and the clinical data were reviewed by one of us, a board-certified expert in neurology and clinical

neurophysiology. The clinical diagnosis was carefully re-considered with special awareness to the fact that severely ill patients may have altered consciousness of non-epileptic origin and/or ambiguous EEG patterns.[11–15]

EEGs had been recorded by the same digital equipment (Brain Quick System Plus, Micromed, Italy), from the 19 standard electrode positions of the 10–20 system and both earlobes against the physical reference at Fpz, and recomputed against a mathematical linked-ears reference. The EEG signal was filtered at 0.1 and 33.6 Hz, sampled at 128 per second and underwent 12 bit on-line digitization. The EEG technician who observed the ictal pattern alarmed the physician who checked and described the patient's condition and gave intravenous diazepam to stop AS.

Intravenous diazepam administration led to rapid improvement of the motor and mental functions, along with simultaneous disappearance of ictal EEG activity in all of the patients. EEG segments after diazepam administration were not quantitatively analyzed.

In the forthcoming time period the patients were treated according to their individual disease conditions. EEG was repeated within 48 h after AS but no ictal activity appeared. However, these recordings did not fit the criteria for quantitative EEG analysis because of biological artifacts.

2.2. Quantitative EEG analyses

Sixty, consecutive, two-second epochs of the individual ictal patterns were selected and processed to a software package that included NeuroGuide Deluxe (version 2.7.1.0), Low Resolution Electromagnetic Tomography (LORETA) and LORETA Source Correlation (LSC; www.appliedneuroscience.com). Fast Fourier Transform-based computation resulted in absolute spectral power values (microvolts squared) for very narrow bands (VNBs) of 1 Hz bandwidth across the 1–25 Hz frequency range. Absolute spectral values were age-corrected and *Z*-scored according to the NeuroGuide Normative Database.[16] Investigating *Z*-scored EEG spectra is an explorative analysis approach to highlight the VNBs where major spectral peaks and humps (indicating major deviation from the normative mean) occur. Selecting VNBs of interest for further analysis is more useful than analyzing a priori defined broad bands. This approach is appropriate for LORETA (but not for LSC) analysis, as described further down.

2.3. LORETA analysis

LORETA is a method to localize multiple distributed sources of EEG activity in three-dimensional space.[17] LORETA demonstrates the synchronously activated neuronal populations underlying EEG activity by computing their cortical localization from the scalp distribution of the electric field. This is called solving the inverse problem of the EEG. The LORETA inverse solution is based on the "smoothness" assumption, which means that neighboring neuronal generators show highly correlated activity in terms of orientation and strength. The smoothness assumption is based on neuroanatomical and electrophysiological constraints. In order to mathematically mitigate the disturbing effects of the electrically conducting layers between the cortical surface and the electrodes, LORETA computes the inverse solution within a three-shell spherical head model including scalp, skull, and brain. The brain compartment of this model was restricted to the cortical gray matter and hippocampus, according to the Talairach Brain Atlas[18] digitized at Montreal Neurological Institute. The gray matter compartment is further divided in 2394 voxels, which allows a spatial resolution of 7 mm. LORETA computes current source density (CSD, Ampers/meters squared) for each voxel. For the sake of brevity, this is called "activity" in the LORETA literature and in this paper. The consistency of LORETA with physiology and localization has been validated by several authors as summarized in a review paper.[19] Importantly, LORETA based on 16–28 channel EEG recordings localizes the sources of maximum EEG activity concordantly to the reference localization methods (positron emission tomography, functional MRI, MRI diffusion spectral imaging, intracranial EEG recordings) when the electrical source distribution is "neurophysiologically smooth"[19,20]; when delta, theta and alpha frequencies that subserve global integration of higher cerebral functions and penetrate the entire hemispheric volume are addressed[21] and when the signal to noise ratio is high, as in epileptic synchronization.[22–25] CSD is related to spectral power, so LORETA solutions were generated only for the VNBs of interest, where the greatest *Z*-scored spectral power values occurred. In order to reduce the vast amount of the numerical data and to get an average estimate of what happens in the designated frequency bands of interest, we computed average LORETA solutions for the adjacent VNBs that showed similarly abnormal *Z*-power values, appearing as spectral humps, rather than peaks in spectral analysis (for example, see Fig. 2). Also the CSD values were age-adjusted and *Z*-scored, according to the LORETA normative database.[26]

2.4. LORETA Source Correlation (LSC) analysis

LSC analysis is a recently developed, LORETA-based method to investigate the magnitude of intrahemispheric EEG functional connectivity (EEGfC) among cortical regions. LSC analysis means computing the temporal covariance or correlation of CSD between two cortical areas across successive two-second epochs over the investigated sample (Fig. 1). Correlating the activity of localized sources is a useful alternative to correlating quantitative EEG variables measured at scalp electrodes, offering a deeper understanding of cortico-cortical connectivity.[27] The Pearson product correlation coefficient (*R*) is a valid measure of oscillator coupling, especially when a relatively long interval of time is analyzed. Authors who compared the sensitivity and reliability of several methods concluded that Pearson correlation is a robust method being sensitive to all the investigated coupling parameters and does not require specific assumptions about the model.[28] In this study we followed the design described in a pioneering LSC investigation.[29] In that study, the effect of the point spread on CSD estimates was minimized by clustering hundreds of nearby voxels into 33 ROIs (regions of interest) in each hemisphere. Each ROI corresponded to a cortical gyrus, according to standard anatomical

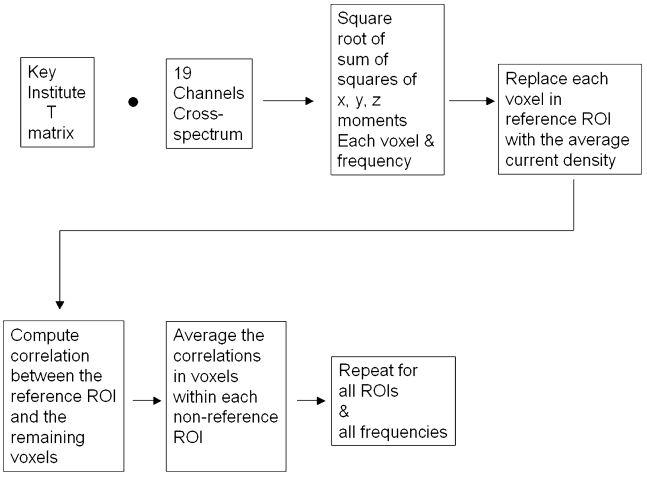

Fig. 1. The flowchart of computing LORETA Source Correlation.
After Thatcher et al.,[29] slightly modified. With permission of the authors.

parcellation. However, the *Z*-scored LSC approach we used in this study operates with 23 ROIs in each hemisphere. Reducing the number of ROIs was necessary to achieve adequate approximation to Gaussian. Thus the individual EEGfC values among the 2×23 ROIs were compared to the normative EEGfC values among the same, 2×23 ROIs. With this number of ROIs, the magnitude of a ROI corresponds to a great gyrus or a cortical area that comprises two or three smaller gyri. Details are available at a website (Thatcher, www.appliedneuroscience.com). Unlike LORETA results, LSC results are not derivatives of EEG spectral power. So, EEGfC was evaluated in all VNBs in the 1–25 Hz frequency range, but only the statistically abnormal results (outside the ± 3 *Z* range) were presented in this study.

2.5. Connectome visualization

The EEGfC data were plotted using BrainCON (www.mini-petct.com/braincon), a software developed in house for the purpose of interactive visualization and processing of multimodal brain connectivity data. The plotting method is based on a standard brain template and the spatial definition of LORETA regions as follows. After segmenting the outer surface of the gray matter of the MNI-152 template,[30] 3D surface models separately for the left and right hemispheres were reconstructed and spatially smoothed. Axial, coronal and sagittal views of these surface models were rendered in 3D. Above these "glass brain" renderings, ROIs were visualized by spheres. The positions of these spheres were calculated by an *x*, *y* and *z* directional orthogonal projection of the spatial center of gravity of LORETA regions,[31] corresponding to the axial, coronal and sagittal views, respectively. The *Z*-scored correlation coefficients were displayed in color-coded mode.

2.6. Z-Statistics

Age-adjusted, *Z*-scored results were computed for all the individual analyses, according to the above-specified normative databases. Quantitative EEG databases are independent of geography, race and sex, and can be used all over the world provided that technical standards are accepted.[32] *Z*-Statistics is a proper way to estimate the deviation of an individual quantitative EEG value from the normative mean ($Z = 0$) of the same age group. Only results outside the ± 3 *Z* range are labeled as "abnormal" and presented in this study.

3. Results

3.1. EEG and spectral analysis results

In five patients the ictal records showed high voltage (120–450 μV) generalized, bilaterally synchronous and symmetrical EEG activity composed of regular or irregular slow waves in the 1–6 Hz frequency band, with intermingled spikes, sometimes multispikes. Two patients showed atypical, irregular, 2–4 Hz spike–wave activity with multispike components. In each case, maximum voltage was found in frontal, central and temporal derivations symmetrically. The electric field showed antero-posteriorly decreasing voltage gradient in all instances. No focal abnormality or hemispheric asymmetry appeared. The frequency spectrum showed very similar characteristics in all patients. The greatest *Z*-scored spectral power occurred in the 1–6 Hz and 12–14 Hz frequency bands (Fig. 2). The main spectral peak was found at 5 Hz with similar localization: T4 in five patients, F7 and T3 in Patients 5 and 6, respectively.

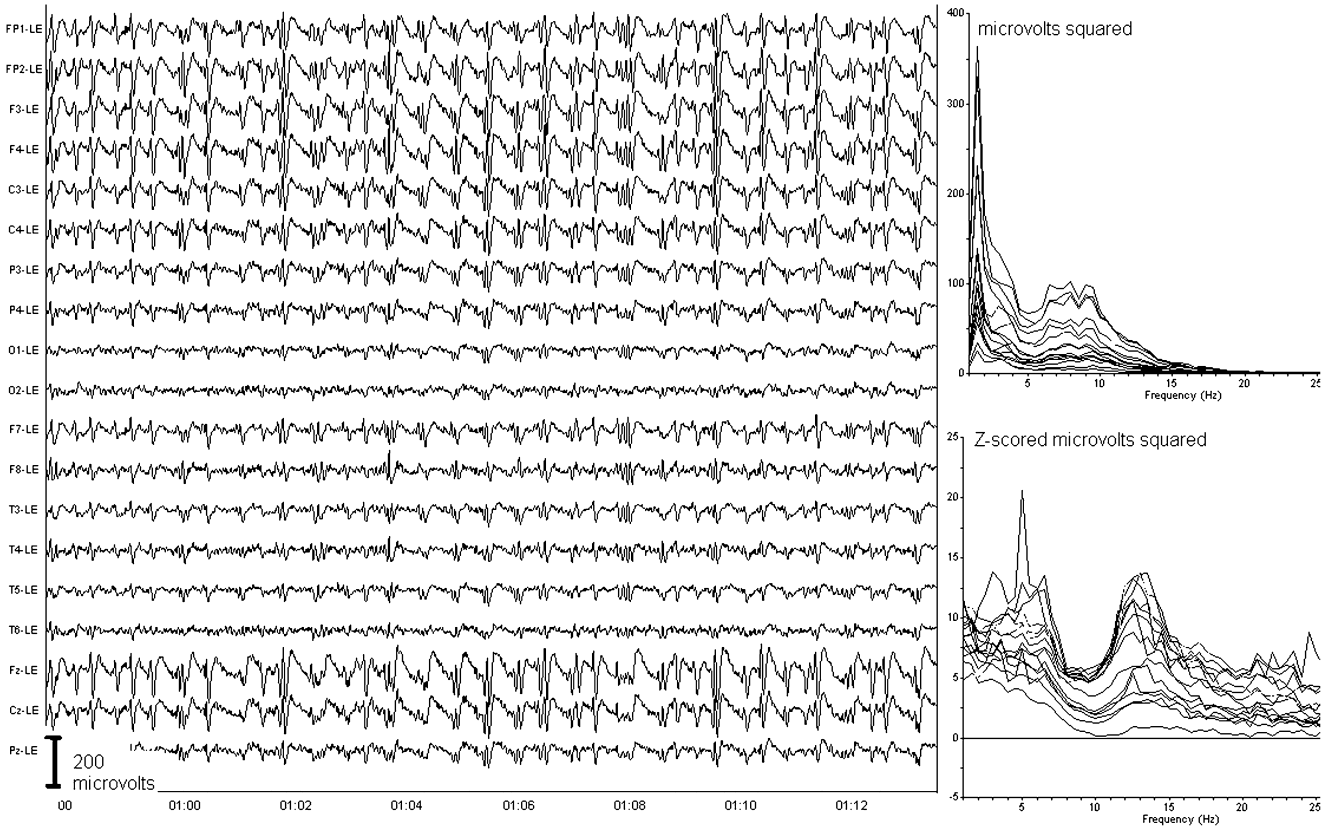

Fig. 2. An example for AS, ictal EEG pattern (Patient 1). LE = mathematically linked ears reference. Absolute power spectrum (right, top), *Z*-scored absolute power spectrum (right, bottom). This case was representative of the group insofar as the *Z*-spectrum showed two frequency bands of uppermost increased power (1–6 Hz and 12–14 Hz). The main peak at 5 Hz corresponds T4 derivation.

Table 2
Abnormal LORETA activity in the patients. The four highest *Z*-values within the averaged 1–6 Hz range, and the highest *Z*-value within the 12–14 Hz frequency range are given. L = left hemisphere; R = right hemisphere.

Pt. no.	Age (sex)	Maximum LORETA abnormalities		*Z*-Score
		Frequency	Gyrus	
1	50 (M)	1–6 Hz	Anterior cingulate L,R	7.7
		1–6 Hz	Subcallosal area L,R	7.2
		1–6 Hz	Straight gyrus, medial frontal gyrus (L,R)	6.7
		1–6 Hz	Parahippocampal L,R	6.2
		13 Hz	Anterior cingulate L,R	7.0
2	82 (M)	1–6 Hz	Insula L	6.4
		1–6 Hz	Parahippocampal R	6.2
		1–6 Hz	Fusiform L	5.9
		1–6 Hz	Anterior cingulate L,R	5.9
3	69 (F)	1–6 Hz	Anterior cingulate L,R	8.8
		1–6 Hz	Subcallosal area L,R	8.4
		1–6 Hz	Parahippocampal, R	8.1
		1–6 Hz	Insula L	8.1
		12 Hz	Anterior cingulate L,R	5.8
4	82 (F)	1–6 Hz	Anterior cingulate L,R	7.6
		1–6 Hz	Middle part of the cingulate gyrus L,R	7.6
		1–6 Hz	Inferior and middle temporal R	7.2
		1–6 Hz	Subcallosal area L	7.1
		13 Hz	Superior frontal L,R	4.1
5	32 (F)	1–6 Hz	Parahippocampal R	6.6
		1–6 Hz	Anterior cingulate L,R	6.3
		1–6 Hz	Middle part of the cingulate gyrus L,R	6.2
		1–6 Hz	Superior frontal L,R	5.7
		14 Hz	Anterior cingulate L,R	6.2
6	42 (M)	1–6 Hz	Insula R	8.6
		1–6 Hz	Parahippocampal R	8.6
		1–6 Hz	Anterior cingulate L,R	8.1
		1–6 Hz	Insula L	8.1
		12 Hz	Anterior cingulate L,R	4.6
7	56 (M)	1–6 Hz	Parahippocampal R	7.9
		1–6 Hz	Subcallosal area R	7.6
		1–6 Hz	Uncus R	7.6
		1–6 Hz	Anterior cingulate L,R	7.2
		12 Hz	Anterior cingulate, medial frontal L,R	5.0

3.2. LORETA results

LORETA solutions were generated for the two bands of interest (1–6 Hz and 12–14 Hz) for each patient. Increased ($Z > 3$) LORETA activity characterized the great majority of the cortex, with antero-posteriorly decreasing CSD gradients in all patients. Increased activity did not extend to the occipital cortex in three patients. The localization of the four greatest *Z*-values within the 1–6 Hz and the 12–14 Hz bands were tabulated (Table 2). The individual, 1–6 Hz LORETA solutions showed some topographical diversity, but the 12–14 Hz solutions were topographically very similar. Therefore, all the 1–6 Hz figures but only one of the 12–14 Hz solutions (for Patient 1) were graphically demonstrated (Fig. 3). The greatest *Z*-values in the 1–6 Hz band were localized to medial temporal structures (parahippocampal gyrus, hippocampus), medial frontal cortex (the very rostral part of the anterior cingulate), the subcallosal area and the insula. Only Patient 4 did not show increased activity in the medial temporal area. Additional areas of increased LORETA activity in the medial-basal frontal or lateral temporal cortex were individual features. In five patients, maximum scores in the 12–14 Hz frequency band were localized to the anterior cingulate bilaterally. This area was topographically non-contiguous with the very rostral area of this gyrus where 1–6 Hz activity peaked. Two patients did not display abnormal *Z*-score in this band. These findings did not show any correspondence with the neurological deficits and the focal CT abnormalities.

3.3. LSC results

LSC analysis resulted in very dissimilar topographical EEGfC patterns. Patients 1, 2 and 7 displayed a lot of increased EEGfC values among several, frontal, temporal, parietal and occipital ROIs (Fig. 4). Overall, more right then left hemispheric abnormalities emerged. Patients 3 and 6 showed one to five abnormal findings that seemed to be topographically random-like and did not outline a network. Patients 4 and 5 did not display abnormal *Z*-scores at all. No topographical relationship was found between the LSC results and the clinical and imaging findings.

4. Discussion

AS was caused by combinations of multiple, structural and biochemical cerebral abnormalities in our patients, which is common in neurological practice.[5,33] Our patients are similar to the patients who were pooled under the heading "NCSE proper".[34] These cases are characterized by disturbed higher cortical functions, the lack of spontaneous movements, unresponsiveness and mutism but not coma. Our patients who had no prior history and presented with de novo AS of late onset are similar to those described in a previous report of 11 cases.[35] The authors suggest that absence status of middle age or late onset results from the addition of various epileptogenic factors. In fact, our cases also suggest the additive effect of seizure-provoking influences. Another term that fits the presented cases is "dialeptic status

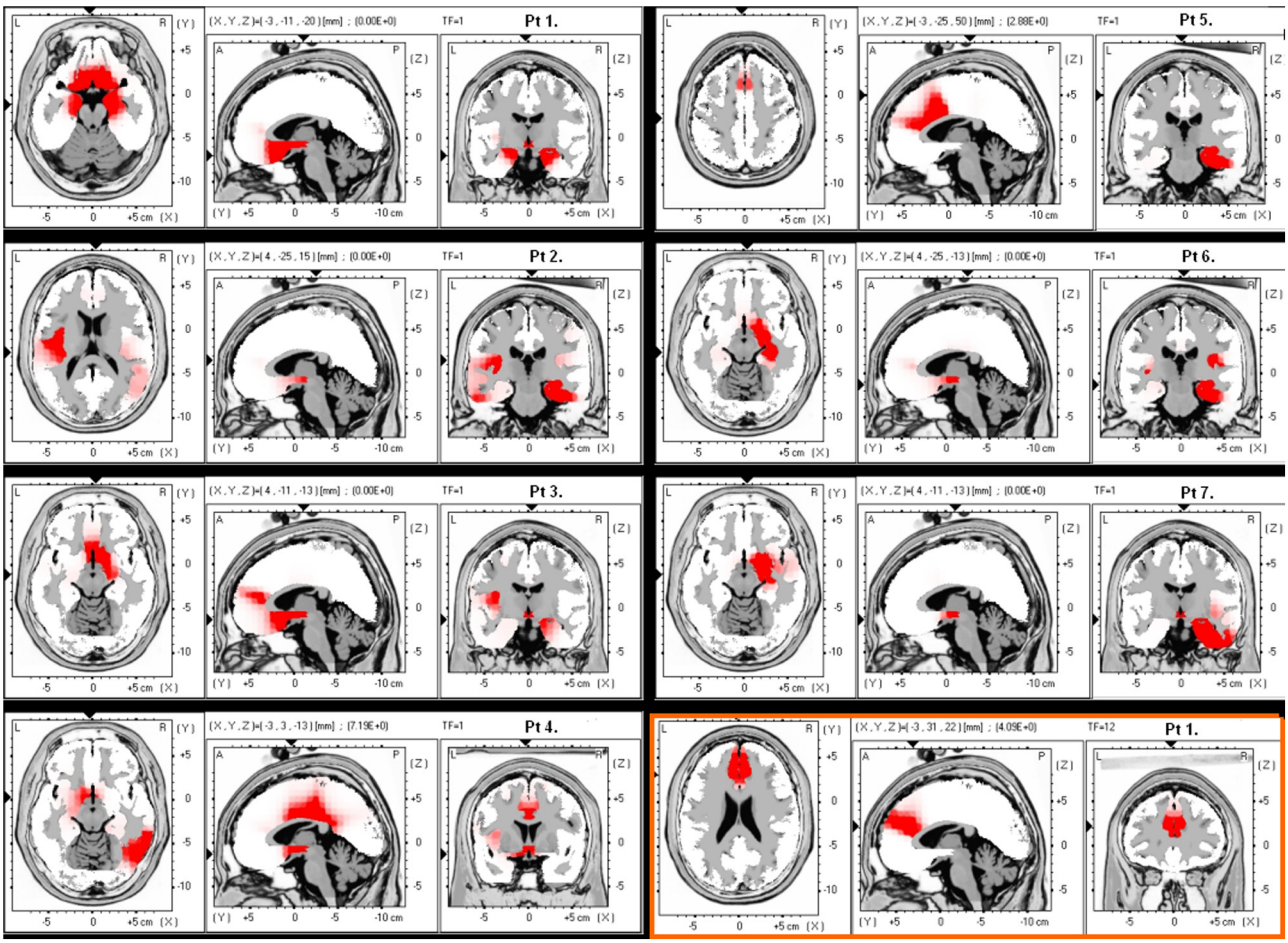

Fig. 3. Individual LORETA solutions. All but one plot are generated from the 1–6 Hz data; they give a raw visual estimate of the areas where the four greatest *Z*-values occurred. Left column, top-down: Patients 1–4. Right column, top-down: Patients 5–7. A single plot was generated from the 12–14 Hz values of Patient 1 (orange framed, in the right, lower corner). No common *Z*-score color scale exists for the plots. Numerical results are given in Table 2.

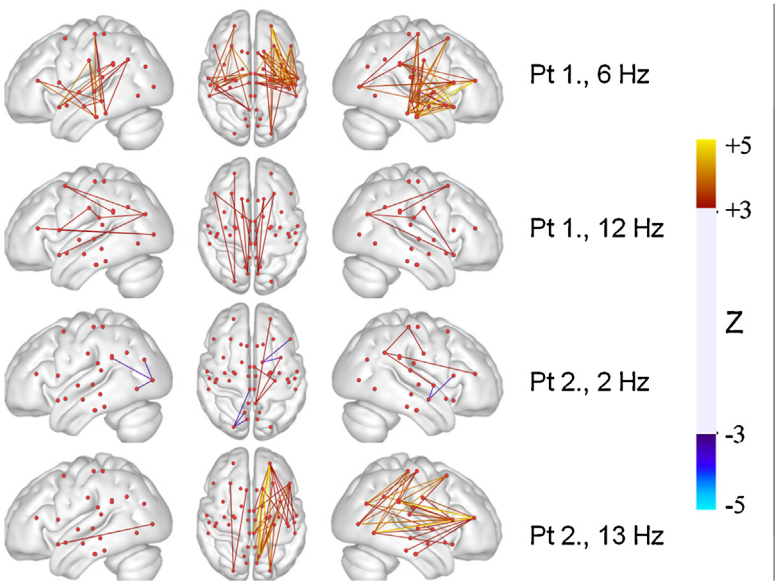

Fig. 4. Individual LSC results for Patients 1 and 2. These patients (and Patient 7) displayed a lot of abnormal EEGfC values. VNBs where the greatest number of abnormal *Z*-values occurred are presented.

epilepticus" characterized by absent voluntary movements and disturbed consciousness. However, disturbed consciousness is not an absolute criterion because unresponsiveness significantly hinders the evaluation of mental functions.[36] Also idiopathic generalized epilepsy (IGE) can give rise to generalized AS. However, none of our patients presented with seizures types (absences, myoclonia) that are usual in IGE syndromes. Furthermore, the term "idiopathic epilepsy" is not compatible with the presence of epileptogenic, structural and metabolic abnormalities. Only one patient had absence epilepsy in childhood but reached terminal remission many years ago.

De novo AS emerging in patients with multiple disease states requires pondering the relative contribution of genetic predisposition, chronic brain pathology and recent, seizure-provoking factors. The remote history of acute symptomatic seizures or epilepsy (even if in remission) suggests the persistence of genetically determined seizure liability in Patients 1–5. Structural pathology that impairs the integrity of the brain and may increase seizure susceptibility was proven in Patients 1–4 and 7. In addition, abnormal brain biochemistry was suspected in Patients 1 and Patient 5 who suffered from mental retardation, depression and alcohol abuse, respectively. Also these factors are known to contribute to increased seizure susceptibility.

Seizure-precipitating factors that might transiently lower the seizure threshold occurred in all but one patients as follows: intracerebral hematoma and surgery (Patient 2), encephalitis (Patient 6), upper airway infection (Patients 1 and 5), purulent uroinfection (Patient 4) and unexplained fever (Patient 7). As to the latter cases, the contribution of peripheral inflammation to seizure susceptibility has been realized recently.[37] So, Patient 3 was the only in whom no seizure precipitating factor was suspected or proven. However, very recent or minor ischemic strokes may escape detection by cranial CT, and routine laboratory screening is not able to detect all the possible seizure-provoking metabolic influences.

4.1. Spectral and LORETA findings

Spectral analysis disclosed that the 1–6 Hz and 12–14 Hz bands are of main interest in our patients. Increased activity in the 12–14 Hz and 1–6 Hz frequency band correspond to the spike and the wave components of the AS pattern, respectively. This is the first investigation that localized the cortical sources of the AS pattern in the three-dimensional space. The findings indicate that AS is very similar to absence seizures where the generators of the spike and the wave components are topographically separated.[38–40]

In the 1–6 Hz range, LORETA localized widely distributed sources of abnormally synchronized activity to frontal, temporal, parietal areas in all of the patients, and also to the occipital areas in four of them. However, the greatest abnormalities were found in the medial temporal structures, anterior cingulate, subcallosal area and the insula. These areas belong to the cortical compartment of the limbic system.[41] They form a strongly interconnected network in healthy persons and epileptic patients.[42–45] Epileptic synchronization within this network may give rise to focal nonconvulsive seizures starting from frontal or temporal sites,[46–48] "generalized" absence seizures that actually start in the medial-basal prefrontal cortex[39,49] and intermediary seizure types called "frontal-onset absences".[47,50] The common core symptoms of these seizure types suggest that also their anatomical substrates are overlapping. Our LORETA findings suggest that the investigated AS patients belong to this spectrum of seizures. Despite the diversity of the etiological factors, the inter-individually consistent LORETA abnormalities suggest that the above-mentioned cortical components of the limbic system responded as a whole to the ictogenic influences.

The greatest LORETA abnormality in 12–14 Hz band occurred in the medial frontal cortex (anterior cingulate). Increased local excitation in this area may give rise to generalized spike–wave paroxysms and absence seizures,[51] and may be important in generating the spike–wave pattern in AS, too. Spike–wave seizures start with the spike component but clinical symptoms are mainly related to the wave.[52] We claim that this duality refers to our AS patients as well. If so, increased activity in the 12–14 Hz band may refer to the area of seizure onset while the wave components (1–6 Hz) correspond to the clinical symptoms.

4.2. LSC findings

EEGfC has not been analyzed in long-lasting seizure states with generalized spike–wave patterns. Functional connectivity was analyzed in absence epilepsy but the results refer to the preictal-ictal transition and the early ictal period,[53–56] so comparison with our findings is limited. The essence of these studies can be summarized as: increased EEG/MEGfC among multiple, frontal and extra-frontal cortical areas; the topographically diffuse abnormalities indicate network dysfunction rather than the cardinal role of any part of the cortex; frequency-dependence of the results; great inter-individual variability of the findings. The same general characteristics were found in three of our AS patients (Patients 1, 2 and 7) as well. The lack of significant EEGfC abnormalities in the remaining four patients remain an enigma. It is reminiscent of the ictal functional MRI abnormalities in absence seizures: ictal BOLD (blood-oxygen-level-dependent) changes are inter-individually very dissimilar and no changes were detected at all in a few patients.[57] As a possible explanation, ictal EEG activity does not mean that all the neurons or EEG generators within the affected cortical areas are abnormally synchronized.[58] One can speculate that differences in the number of synchronized generators might contribute to the great inter-individual variability of the EEGfC and functional MRI findings alike. As another possibility, dissimilar disease condition may be responsible for the dissimilarity of the EEGfC findings in our patients. EEG/MEGfC may be disturbed by single cerebral lesions,[59] multiple small lesions,[60] degenerative cerebral disorders,[61] seizures[62,63] and neuroactive drugs.[64] We tried to topographically correlate the individual LSC findings to the individual, structural abnormalities but no evidence for causal relationship was found. Furthermore, there is some evidence that abnormal network activity emerges with elapsing time rather than promptly after the cerebral insult.[65] Re-investigating EEGfC in the post-AS period would be interesting. Unfortunately, EEGs recorded within 48 h after AS were not of good quality, so no "baseline" results are available. These issues need further investigations.

4.3. Hemispheric asymmetry

Both LORETA and LSC demonstrated right hemispheric preponderance of abnormalities. No explanation for this asymmetry exists. Physiological differences in hemispheric organization can hardly explain the findings because *Z*-statistics compares each individual value to the normative mean of the corresponding hemisphere. Neither the clinical and imaging data nor the spectral and LORETA results explain asymmetrical EEGfC findings. However, the patient sample was too small to investigate this issue. Increased LORETA activity and increased intrahemispheric functional connectivity might be related to increased seizure propensity. Thus the right hemispheric predominance of the abnormal findings is in accordance with the EEG and magnetoencephalography (MEG) results of two research groups who reported that the majority of absence seizures start from the right hemisphere.[49,66]

4.4. Limitations of the study

The main limitation of the study is related to the localizing precision of LORETA, particularly when the 19 standard electrodes and the standard head model are used. The precision of source localization depends on the number of electrodes, their spacing, the head model, individual skull and brain anatomy and the assumptions of the inverse solution method. In fact, using 19 electrodes and the three-shell head model are not state-of-art techniques of source localization. However, the risk of incorrect localization is sometimes overemphasized in the literature. LORETA frequently fails in non-biological environments like simulation studies and theoretical frameworks, where small and well-demarcated sources are considered. We mean that the precision of source localization is not equally important in all situations. Rather, it depends on the task and the biological system and condition that is evaluated. In Section LORETA analysis we quoted a few references[19–25] to demonstrate why the described EEG design and LORETA presumably perform well in the present study. In brief, LORETA correctly localizes the gravity of center of the abnormality with 19 electrodes and the standard head model in real situations (intracranial EEG- and cross-modal validations, with special reference to epileptic synchronization and status epilepticus). The object of this study was a real biological situation (AS), where abnormal activity emerged in widespread, topographically contiguous cortical areas. In addition, EEG frequencies that penetrate the entire brain were investigated. Intracranial EEG studies demonstrated that the voltage and CSD gradients of ictal EEG activity are smooth. That is, blurring the borders of abnormal activity (an argument usually cited against LORETA) is presumably not a great problem if also the borders of the abnormality are smooth. Also the signal-to-noise ratio of the high voltage ictal activity was excellent in this study. However, individual variability may be important and unpredictable effects may always appear, so we described the results at the level of ROIs, but discussed them at greater (lobar, sub-lobar) spatial scales. Importantly, not only the maximum CSD abnormality, but also the great majority of the four greatest *Z*-values were taken into consideration for each patient and hemisphere. Collective interpretation of the 2×4 values strongly suggests that the areas of maximal CSD are within prefrontal and medial temporal parts of the cortex that functionally belong to the limbic system.

In theory, the results may be influenced by the chronic disease states and acute cerebral insults enumerated in Table 1. Some of them may cause EEG abnormalities in standard EEG recordings. However, we think that the high voltage AS pattern masked other abnormalities, so the LORETA results are reliable. On the other hand, lesional and drug effects on EEGfC may be real problems. Unfortunately, little is known about the effects of diverse disease conditions on EEGfC.

5. Conclusions

Quantitative EEG analysis of AS demonstrated the three-dimensional distribution of the generators of abnormal EEG activity within the 1–6 Hz and 12–14 Hz frequency bands. LORETA disclosed that AS resulted from abnormally synchronized generators within widespread cortical areas or within the entire cortex. However, the uppermost synchronized generator ensembles were invariably localized in the same set of limbic cortical areas. The findings were independent of the combinations of chronic and recent neurological disorders and seizure-precipitating factors in the patients.

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